REMARKS

The claims have been amended to set forth the invention more clearly and to eliminate unnecessary dependent claims. Claim 13 has been extensively amended to better describe the method of the invention. The requirement that the method be carried out on a computer has been deleted; although it is unlikely that the claimed method could, in a practical way, be carried out absent using a computer, the method itself is new and unobvious regardless of how it is performed. Support for the amendments to claim 13 is found, for example, in Example 1 of the specification and throughout the specification. Support for the amendment to claim 14 is found on page 20, lines 15-21 and on page 59, lines 17-22.

Claim 34 has been amended to depend from claim 1 as the system, which involves a computer, simply carries out the method of claim 1. As is clear from page 54, lines 10-13, a single computer or connected computers may be used. Claim 35 has thus been canceled as redundant. Claim 60, directed to a computer program has been amended to conform to claim 13 and claim 81 has been amended to depend from claim 60 as claim 81 simply claims an article of manufacture which comprises a computer medium having the computer program described in claim 30.

It will be noted that throughout the claims, "nucleotide" has been substituted for "gene" for clarity; the nucleotide sequence to be targeted is designated as a "first" nucleotide sequence; the known nucleotide sequence that is used as the basis for the method is designated the "second" nucleotide sequence.

The remaining amendments are simply for clarity and style and do not affect claim scope or substance. No new matter has been added and entry of the amendment is respectfully requested.

The Invention

The invention is directed to a novel procedure for obtaining primers that will permit cloning of a nucleotide sequence in an organism that confers a desired phenotypic characteristic. This is done by analogy to sequences known to be associated with this phenotypic characteristic in a multiplicity of organisms and taking advantage of conserved sequences among these cataloged sequences.

Thus, the method itself comprises the steps of providing a nucleotide sequence as a starting point (the "second" nucleotide sequence) where the nucleotide sequence is known to confer one or more desired phenotypic characteristics in the organism in which it resides. Using this "second" nucleotide sequence, databases which provide correlations between phenotypic characteristics and sequences, preferably in a multiplicity of organisms, are searched for matches to the "second" sequence. This will result in a list of sequences known to be associated with the desired phenotypic characteristic. These sequences can be prioritized according to their similarity of alignment with the "second" nucleotide sequence so that sequences which do not appear to be closely related to the second nucleotide sequence can be discarded. The prioritized sequences are then aligned and regions that match are noted and used as the basis for designed primers. The entire method can be performed on an integrated computer system which provides both the databases and the steps for performing the method. The method is useful in obtaining genomic information to manipulate organisms in respect of particular phenotypic characteristics that may be desirable, such as retrieving genes responsible for toxin receptivity in insects or retrieving the targeted gene in humans that matches a target of pharmaceutical in mice.

The Restriction Requirement

Applicants are very grateful and want to express their appreciation to the Examiner for withdrawal of the restriction requirement as it pertained to Groups III-VI. The willingness of the Examiner to review all of claims 13-82 as directed to the same invention is much appreciated by applicants.

The Objection to the Specification

This has been corrected by amendment.

The Rejection Under 35 U.S.C. § 101

Claims 13-33 were rejected as directed to non-statutory subject matter; it is noted with appreciation that claims 34-82 are free of this rejection.

The basis for this rejection appears to be that the result of the method is not immediately useful. But this is not the case. It appears acknowledged that it is useful to design primers for targeting a desired nucleotide sequence as long as a computer is used in claims 34-82; it is unclear why the method would be any less useful if not performed on a computer. In any event, applicants do not understand why they should specify "what types of sequences are being analyzed." As pointed out above, there are multiple instances where it is desirable to find, in an organism, the nucleotide sequence encoding a protein that will have a desired phenotypic result so that that gene can be manipulated in the organism. The method is directed to obtaining *any* nucleotide sequence of interest; it does not matter to the method whether the sequence sought is useful as a target for a toxin, a target for a therapeutic, a protein which confers an enhanced immune response, or any other of a multiplicity of outcomes that can be obtained by manipulating genes. It should no more be necessary to catalog all the possible reasons that one

might wish to retrieve a desired nucleotide sequence than to catalog all the possible compounds that might be separated by a new chromatographic technique. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

The Rejections Under 35 U.S.C. § 112, Paragraph 2

A number of objections were raised based on this provision.

With respect to claim 13 (and it is assumed, claims 34, 60 and 81), inquiry is made as to what the important "phenotypic" characteristics are. As noted above, any desired phenotypic characteristic may be the subject of the present method. The invention does not lie in finding a phenotypic characteristic of interest - there are so many of these that it would be a meaningless exercise to catalog them all. One might want, for example, to enhance the production of cytokines, the production of antibodies, the production of receptors for certain ligands, and on and on. It is believed that in the context of the claimed method, this term is clear.

With respect to these same claims, the Office then questions the process of "selecting one or more gene sequence." The amendments to these claims address this question; the process simply starts with a nucleotide sequence known to result in the phenotypic characteristic of interest. This is just the starting point for the gene mining method of the invention.

As to "extracting a cataloged gene sequence," again, it is believed the amendment clarifies this; the databases are reviewed for nucleotide sequences that are correlated, in the databases, with the phenotypic characteristic desired.

The amendment to the claims clarifies that the prioritization is based on the successful alignment to the "second" nucleotide sequence; this permits sequences which confer the desired phenotype, but are so dissimilar as to represent different gene families to be eliminated from

consideration. Either the criterion of the closest actual matches or the closest pattern matches could be used; the method is simply directed to providing the cataloged sequences that have the closest relationship to the starting, second nucleotide sequence.

With respect to claims 14, 36 and 61, "filtering" is done by eliminating matches that are not determinative of the desired characteristics, as explained on page 20, lines 15-21. This could be accomplished using BLAST, but the specific algorithm used is not critical to the invention.

With respect to claims 21-22 and their corresponding claims 43-44 and 68-69, these claims have been canceled.

With respect to claim 23 and corresponding claims 45 and 70, again, the specific statistical test is not a critical feature of the invention; any recognized statistical test can be used. The rejections of claims 56-57 and 68, are obviated by cancellation of these claims.

In view of the amendments and discussion above, the rejections under this provision of the statute may properly be withdrawn.

The Rejections Under 35 U.S.C. § 102

It is first noted, with appreciation, that claims 19, 41 and 66 are not rejected over the art. They are also not subject to rejection under 35 U.S.C. § 112, second paragraph; only claim 19 is included in with rejection under 35 U.S.C. § 101. Thus, there appears to be no outstanding rejection of claims 41 or 66.

Claims 13-14, 16, 20-30, 32-36, 38, 42-52, 54-61, 63, 67-77 and 79-82 were rejected under 35 U.S.C. § 102(e) as assertedly anticipated by Messier, *et al.*, U.S. 6,274,319. The Office is correct that both Messier and the present invention describe methods for identifying sequences that are associated with phenotypic characteristics. The similarity ends there, however.

Messier describes a simple comparison between a gene or a protein in a domesticated organism with that in a wildtype ancestor. This permits identifying an evolutionarily significant change in a nucleotide sequence of a domesticated species as compared to the wildtype ancestor. There is no discussion in Messier of designing primers based on matching sequences from a multiplicity of organisms described in cataloged databases. The only mention of primer design in the cited sections is in column 10, paragraph 3, where it is clear that primers are designed from the candidate domesticated organism cDNA sequence; they are not designed from sequences extracted, prioritized, and aligned from cataloged databases as required by the invention. The section in paragraph 3, in column 11 of Messier, noted by the Examiner, is simply a comparison of wildtype sequence to that of the domesticated organism. No sequence alignments for a multiplicity of extracted databases is described there either.

The other portions of Messier as cited by the Office, column 5, paragraphs 1 and 2, column 6, paragraphs 2 and 3 and column 9, paragraph 4 do not appear to relate significantly to the present invention at all. Paragraphs 1 and 2 in column 5 describe methods of identifying an agent that can modulate the relevant trait in a domesticated organism by contacting the agent with a model system. Paragraph 2 relates simply to the comparison of sequences from the domesticated species with that of the wildtype species; again there is no disclosure of extracting a multiplicity of sequences from databases that correlate with a desired phenotype for providing the best matches that are maintained over a large number of representative sequences. Column 6, paragraphs 2 and 3 are directed simply to methods to obtain DNA libraries; column 9, paragraph 4 is a definition of a "target site." It is unclear what any of these sections have in common with the present invention which requires a series of specific steps not described Messier individually or in relationship to each other as required in the present invention.

It will perhaps be helpful to remind the Office that the present invention requires these specific steps - 1) using a starting nucleotide sequence of known phenotypic association; 2) using this sequence to mine databases for a multiplicity of sequences correlated with the desired phenotypic characteristic, and 3) sorting these so as to winnow the extracted sequences to those most closely related, and then 4) designing primers based on the most closely matched regions.

Thus, independent claims 13, 34, 60 and 81 are free of the prior art; accordingly, any claims dependent thereon are also not anticipated or suggested by the cited document.

In addition, as noted above, "filtering" resides in the process of deleting portions of the sequences from consideration so as to eliminate portions common to unwanted genes. There is no suggestion at all of this process in Messier. (Claims 14, 36 and 61.)

Accordingly, this basis for rejection may properly be withdrawn.

Claims 13-15, 17-18, 23-27, 39-40, 45-55, 57, 60-62, 64-65 and 70-82 were rejected under 35 U.S.C. § 102(b) as assertedly anticipated by Sabatini, *et al.,* U.S. 5,966,712.

Sabatini does not even relate to a method which involves the step of designing primers for targeting a desired nucleotide sequence that confer a desired phenotypic characteristic. Sabatini is only concerned with methods of comparing sequence libraries. There is no description in Sabatini, and the Office has pointed to none, of using a starting nucleotide sequence associated with a particular phenotypic characteristic, using that sequence to extract a set of sequences associated with the same phenotypic characteristic from a cataloged database, aligning and prioritizing the aligned sequences to confine the list to those similar, and utilizing the aligned sequences to design primers representing the most closely matching regions.

Applicants, in reviewing Sabatini, are unable to find any such disclosure. If that disclosure exists, applicants would appreciate their attention being called to the specific locations

in the document which describe this process. It is not believed that referring to the entire section entitled "Detailed Description of the Invention" is sufficient to inform applicants of the asserted anticipatory disclosure. Accordingly, this basis for rejection may also be withdrawn.

CONCLUSION

The claims have been amended to clarify the nature of the invention. The remaining claims are claims 13-19, 23, 25-26, 34, 36-41, 45, 47-48, 60-62, 64-66, 70, 72-73 and 81-82. Although it is stated that no claims are allowed, claims 41 and 66 do not appear to have been included in any of the bases for rejection; claim 19 has been included only with regard to the rejection for non-statutory subject matter.

The rejection for non-statutory subject matter, applied only to claims 13-33, is believed misplaced as the useful results obtained by using the method have been demonstrated. The rejections under 35 U.S.C. § 112, paragraph 2, have been addressed either by amendment or discussion. As demonstrated, neither of the cited documents anticipates or suggests the specific steps required in the claimed method. Accordingly, it is believed that the remaining pending claims are in a position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 524182000200.

Respectfully submitted,

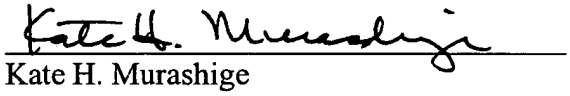
Dated: September 23, 2002 By: 

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EXHIBIT A. - VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

Please amend the paragraph on page 12, lines 9-21 as follows:

The term "x% homology" refers to the extent to which two nucleic acid or protein sequences are complementary as determined by BLAST homology alignment as described by T.A. Tatusova & T.L. Madden (1999), "Blast 2 sequences - a new tool for comparing protein and nucleotide sequences", FEMS MICROBIOL LETT. **174**:247-250 and using the following parameters: Program (blastn) or (blastp) as appropriate; matrix (OBLOSUM62), reward for match (1); penalty for mismatch (-2); open gap (5) and extension gap (2) penalties; gap x- drop off (50); Expect (10); word size (11); filter (off). An example of a web based two sequence alignment program using these parameters is found at [http://www.] the world wide web address:ncbi.nlm.nih.gov/gorf/bl2.html.

In the Claims:

13. (Amended) A method [for targeting gene] to design primers to target a first nucleotide sequence[s having one or more] that results in at least one phenotypic characteristic[s using a computer], the method comprising the steps of:

[selecting one or more phenotypic characteristics;

selecting a gene] providing a second nucleotide sequence that is known to [have] result in the [selected] phenotypic characteristic[s];

[selecting one or more databases containing cataloged gene sequences;]

comparing the [selected gene] second nucleotide sequence to [the cataloged gene] nucleotide sequences cataloged in one or more databases that correlate nucleotide sequences with phenotypic characteristics;

extracting any cataloged gene sequences that contain a portion of the [selected gene] second nucleotide sequence and which result in said phenotypic characteristic;

aligning the [selected gene] second nucleotide sequence to each [portion of the] extracted gene sequence;

prioritizing the extracted gene sequences [based on the] to ensure alignment [of] to the [selected gene] second nucleotide sequence;

[selecting at least one of the prioritized gene sequences based on one or more phenotypic criteria;] and

designing one or more [degenerate] primers based on matching portions of the alleged prioritized sequences to target [the selected-prioritized gene sequences] said first nucleotide sequence.

14. (Amended) The method [as recited in] of claim 13, further comprising the step of filtering the [prioritized gene] extracted nucleotide sequences to eliminate portions common to unwanted genes.

15. (Amended) The method [as recited in] of claim 14, wherein the step of filtering the [prioritized gene] extracted nucleotide sequences removes vertebrate sequences but not invertebrate derived sequences.

16. (Amended) The method [as recited in] of claim 13, further comprising the step of cloning genetic material using the one or more [degenerate] designed primers.

17. (Amended) The method [as recited in] of claim 13, wherein the one or more databases are selected from cataloged [gene] sequences for humans, rats, mice, zebra fish, frogs, Drosophila, nematode, C. elegans, mosquito and bacteria.

18. (Amended) The method [as recited in] of claim 13, wherein [the] said phenotypic characteristic[s include] is expression in insect mid-gut [epithelial cell encoded proteins] epithelium.

19. (Amended) The method [as recited in] of claim 13, wherein the one or more [degenerate] primers are nested.

23. (Amended) The method [as recited in] of claim 13, wherein the step of prioritizing the extracted [gene] nucleotide sequences [based on] to ensure the alignment of the selected [gene] nucleotide sequences is accomplished by using a statistical analysis of the alignment.

25. (Amended) The method [as recited in] of claim 13, wherein the [selected gene] second nucleotide sequence is aligned to each extracted [gene] nucleotide sequence by comparing deduced amino acid sequences.

26. (Amended) The method [as recited in] of claim 13, wherein the [selected gene] second nucleotide sequence is aligned to each extracted [gene] nucleotide sequence by [nucleic acid] comparing the nucleotide sequences.

34. (Amended) A system for designing primers to target[ing gene] a first nucleotide sequence[s having one or more] that results in at least one phenotypic characteristic[s] comprising:

[a] one or more computers collectively having program means thereon for [selecting one or more phenotypic characteristics, selecting a gene sequence that is known to have the selected phenotypic characteristics, comparing the selected gene sequence to the cataloged gene sequences, extracting any cataloged gene sequences that contain a portion of the selected gene sequence, aligning the selected gene sequence to each portion of the extracted gene sequence, prioritizing the extracted gene sequences based on the alignment of the selected gene sequence, selecting at least one of the prioritized gene sequences based on one or more phenotypic criteria, and designing one or more degenerate primers to target the selected-prioritized gene sequences] performing the method of claim 1; and

one or more databases containing the cataloged gene sequences; and

a communication link connecting the computer or computers to said one or more databases.

36. (Amended) The system [as recited in] of claim 34 [or 35], wherein the program means [on said computer] filters the [prioritized gene] extracted nucleotide sequences to eliminate portions common to unwanted genes.

37. (Amended) The system [as recited in] of claim 36, wherein the program means [on said computer] removes vertebrate sequences but not invertebrate derived sequences when the [prioritized] sequences are filtered.

38. (Amended) The system [as recited in] of claim 36, further comprising an apparatus that clones genetic material using one or more [degenerate] primers.

39. (Amended) The system [as recited in] of claim 36, wherein the one or more databases are selected from cataloged gene sequences for humans, rats, mice, zebra fish, frogs, Drosophila, nematode, C. elegans, mosquito and bacteria.

40. (Amended) The system [as recited in] of claim 36, wherein the phenotypic characteristic[s include] is expression in insect mid-gut [epithelial cell encoded proteins] epithelium.

41. (Amended) The system [as recited in] of claim 36, wherein the one or more [degenerate] primers are nested.

45. (Amended) The system [as recited in] of claim 36, wherein the program means [on said computer] uses a statistical analysis of the alignment of the [selected gene] second nucleotide sequence to prioritize the extracted [gene] sequences.

47. (Amended) The system [as recited in] of claim 36, wherein the selected gene sequence is aligned to each extracted [gene] nucleotide sequence by comparing deduced amino acid sequences.

48. (Amended) The system [as recited in] of claim 36, wherein the [selected gene] second nucleotide sequence is aligned to each extracted gene sequence by [nucleic acid] comparing nucleotide sequences.

60. (Amended) A computer program embodied on a computer-readable medium for designing primers to target[ing gene] a first nucleotide sequence[s having one or more] that results in at least one phenotypic characteristic[s], said computer program comprising:

[first selecting] means for [selecting one or more] providing a second nucleotide sequence that results in the phenotypic characteristic[s of said gene sequences;

second selecting means for selecting a gene sequence that is known to have said one or more of said selected phenotypic characteristics];

[third selecting] means for [selecting] providing at least one database containing cataloged [gene] nucleotide sequences therein wherein said catalog correlates sequence to resulting phenotypic characteristics;

[extracting] means for extracting from said at least one database a plurality of cataloged [gene] nucleotide sequences containing a portion of the said [given gene] second nucleotide sequence;

[aligning] means for aligning said [given gene] second nucleotide sequence [to respective ones of] with said cataloged gene sequences;

[prioritizing] means for prioritizing the [respective ones of the] extracted gene sequences [based on the] to ensure alignment [of] with the [given gene] second nucleotide sequence[;

fourth selecting means for selecting at least one of the prioritized gene sequences based on one or more phenotypic criteria]; and

[designing] means for designing one or more [degenerate] primers based on matching portions of the aligned prioritized sequences to target said [at least one selected gene] first nucleotide sequence.

61. (Amended) The computer program [as recited in] of claim 60, further comprising a code segment for filtering the [prioritized gene] extracted nucleotide sequences.

62. (Amended) The computer program [as recited in] of claim 61, wherein the code segment for filtering the prioritized gene sequences removes vertebrate sequences but not invertebrate derived sequences.

64. (Amended) The computer program [as recited in] of claim 60, wherein the one or more databases are selected from cataloged gene sequences for humans, rats, mice, zebra fish, frogs, Drosophila, nematode, C. elegans, mosquito and bacteria.

65. (Amended) The computer program [as recited in] of claim 60, wherein the phenotypic characteristic[s include] is expression in insect mid-gut [epithelial cell encoded proteins] epithelium.

66. (Amended) The computer program [as recited in] of claim 60, wherein the one or more [degenerate] primers are nested.

70. (Amended) The computer program [as recited in] of claim 60, wherein the code segment for prioritizing the extracted [gene] nucleotide sequences based on alignment [of the selected gene] with the second nucleotide sequence is accomplished by using a statistical analysis of the alignment.

72. (Amended) The computer program [as recited in] of claim 60, wherein the [selected gene] second nucleotide sequence is aligned to each extracted [gene] nucleotide sequence by comparing deduced amino acid sequences.

73. (Amended) The computer program [as recited in] of claim 60, wherein the [selected gene] second nucleotide sequence is aligned to each extracted [gene] nucleotide sequence by comparing deduced nucleic acid sequences.

81. (Amended) An article of manufacture comprising a computer [usable] medium having computer readable program code means of claim 60 embodied therein[for targeting gene sequences, the computer readable program code means in said article of manufacture comprising:

computer readable code means for selecting one or more phenotypic characteristics,

computer readable code means for selecting a gene sequence that is known to have the selected phenotypic characteristics;

computer readable code means for selecting one or more databases containing cataloged gene sequences;

computer readable code means for comparing the selected gene sequence to the cataloged gene sequences;

computer readable code means for extracting any cataloged gene sequences that contain a portion of the selected gene sequence;

computer readable code means for aligning the selected gene sequence to each portion of the extracted gene sequence;

computer readable code means for prioritizing the extracted gene sequences based on the alignment of the selected gene sequence;

computer readable code means for selecting at least one of the prioritized gene sequences based on one or more phenotypic criteria; and

computer readable code means for designing one or more degenerate primers to target the selected-prioritized gene sequences].

82. (Amended) The article of manufacture of claim 81, wherein said [article of manufacture is stored on a] medium [selected from a group consisting of] is:

a server, a hard drive, a CD-ROM [and] or a diskette.